nitrogen atom, is optionally substituted with one or more groups selected from alkyl, alkenyl, aryl, aralkyl, alkoxy, aryloxy, acyl, acyloxy, amide, tertiary amine, nitro, or halogen, and may be fused to an one or more additional rings;

with a hexacoordinate complex of a metal selected from tungsten (0), chromium (0), and molybdenum(0),

whereby said complex undergoes a ligand exchange reaction, such that L^1 becomes coordinated to said metal;

wherein said composition is effective to catalyze the enantioselective alkylation of an allyl group bearing a leaving group at its allylic position.

REMARKS

Reconsideration of the rejections set forth in the Office action mailed July 14, 2000 is respectfully requested. Claims 17-23 and 55-58 are pending in the application.

I. Amendments

The specification has been amended to replace a paragraph which was obscured in the copy of the specification submitted with the application. The paragraph inserted is found at page 8, lines 28-34 of the specification of parent application No. 09/213,395, which was incorporated by reference in this application, per the preliminary amendment filed February 7, 2000.

The specification is also amended to correct typographical errors. Support for the correction on page 15 is found in Figures 2C and 2D, which show the structures of ligands **VII** and **VIII**, the latter of which is methoxy-substituted, as stated in the text.

Claim 17 is amended to incorporate the subject matter of claim 55, which more clearly defines the chiral component of the chiral ligand. Claim 17 is also amended to incorporate the subject matter of claim 22, which more clearly defines the binding groups of the ligand, to recite the preferred linkage site of the binding groups (as disclosed at page 9, lines 35-36 of the specification), and to recite a nonprotic solvent (as disclosed at page 11, line 6). Claim 57 has been amended in a similar manner.

No new matter is added by any of the amendments.

II. Rejections under 35 U.S.C. §112, First Paragraph

Claims 17 and 55 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and use the invention without undue experimentation. These rejections are respectfully traversed for the following reasons.

The purpose of the enablement provision is to assure that the inventor provides sufficient information

about the claimed invention to allow a person of skill in the field of the invention to make and use it without undue experimentation, relying on the patent specification and the knowledge in the art. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 1001 1006 (Fed. Cir. 1991). Case law also holds that "enablement is not precluded by the necessity for some experimentation such as routine screening" (*In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, Fed. Cir. 1988).

With respect to how to make the compositions of the invention, the specification provides representative syntheses of chiral ligands (Figs. 2A-2D) and notes that chiral amines, diols and amino alcohols of high enantiomeric purity are commercially available or can be produced via known methods (paragraph bridging pages 8-9). Preparation of the catalytic complex, which is frequently done in situ, is described at pages 10-11.

With respect to the solvent, the specification provides that the solvent should be inert, nonprotic and non-complexing, and provides several examples (THF, ether, toluene, other hydrocarbons, and chlorinated solvents). It would not be beyond the skill of an experimenter in this field to select a nonprotic solvent different from THF or toluene, if desired, and determine whether the results obtained from the reaction were satisfactory.

The specification and claims also provide guidance as to the type of heterocyclic binding groups that should be used and how they are to be attached to the chiral diol, diamine or amino alcohol (i.e. at the carbon adjacent to the binding ring nitrogen). Several examples of binding groups are given at page 9, lines 26-28, including binding groups having two fused rings. One such group, a 2-quinolyl group, was shown to give enantioselectivities similar to those obtained with a 2-pyridyl group (page 15, lines 17-20). Binding groups having various substituents (nitro, methoxy, methyl) were also used successfully (Table 3). It would not be beyond ordinary skill to prepare ligands having binding groups within the scope of the claim (using, for example, a carboxyl-substituted heterocycle, as shown in Fig. 2A) and to test complexes of these ligands for catalytic effectiveness, using procedures described in the specification.

With respect to groups R^1 and R^2 at the chiral centers of the ligand, one of skill in the art would know that groups having high steric requirements, such as bulky groups or closed rings, are typically preferred in frameworks for chiral ligands. Various embodiments are shown in Figs. 2A-2D and 3, including different sized rings, heterocyclic rings, and bulky groups such as phenyl. As shown in Table 3, all were effective in the catalytic compositions of the invention.

The Examiner has not provided sufficient evidence or reasoning, as required in *In re Marzocchi and Horton* (CCPA 1971, 439 F2d 220, 169 USPQ 367), to doubt that the full scope of the claims could not be carried out without undue experimentation. The Office Action implies that the claims would encompass inoperative geometries; however, a variety of ligands within the scope of the claims were shown to be effective, as noted above. Case law also provides, in any case, that the "presence of inoperative

embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." (*Atlas Powder Co. V. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414, Fed. Cir. 1984).

The Examiner also referred to *Ex parte Sizto*, 9 USPQ2d 2081 (BPAI 1988). This decision stated that "Single example...disclosing enzyme catalyst is not sufficient to support claims to catalysts in general, in view of divergence between enzyme and non-enzyme catalysts...". The applicants submit that this case is not comparable to the present application, where numerous working examples are presented, and the claims are directed to Mo, Cr or W complexes having a particular class of ligands, not to "catalysts in general".

In view of the foregoing, the applicants submit that the specification and claims comply with the requirements of 35 U.S.C. §112, first paragraph.

III. Rejections under 35 U.S.C. §112, Second Paragraph

Claims 17, 20-23 and 55 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These rejections are respectfully traversed for the following reasons.

The test for definiteness is whether those skilled in the art would understand the bounds of the claim when read in light of the specification. *Miles Laboratories, Inc. v. Shandon Inc.*, 997 F2d 870, 27 USPQ2d 1123 (Fed. Cir. 1993), *cert. denied*, 510 U.S. 1100 (1994).

The Examiner objected to the claim term "suitable solvent." Independent claims 17 and 57, as amended, recite that the process producing the catalytic composition is carried out in a nonprotic solvent. This term is very familiar to those skilled in the art; thus, it would be a simple matter to tell whether a given solvent fell within the bounds of the claim.

The Examiner also stated that the phrase "derived from a chiral diamine, diol or amino alcohol" is unclear.

Independent claims 17 and 57 recite that the chiral component which is "derived from a chiral diamine, diol, or amino alcohol" has "first and second chiral centers, each substituted with a group X selected from -O- or -NR-". These claims have been amended for additional clarity to recite that the chiral centers are "connected by a direct bond or by a chain of one to three atoms comprising linkages selected from alkyl (carbon-carbon), alkyl ether (carbon-oxygen), alkyl amino (carbon-nitrogen), or a combination thereof".

It would be clear to one skilled in the art, particularly in view of the specification, that these two chiral centers, which are joined either directly or by 1-3 intervening bonds, and which are both substituted

with either oxygen or nitrogen, make up the "diamine, diol or amino alcohol" of the claim. Because the oxygen or nitrogen atoms are further substituted, as described below, the chiral component is "derived from" the diamine, diol, or amino alcohol.

The Examiner has stated that the claim "does not indicate what it [the group X] is further linked to". On the contrary, the claim states that "linked to each said group X, [is] (ii) a heterocyclic binding group Cy_N...".

The Examiner also states that the scope of the heterocyclic binding group is unclear.

This group is defined in the amended claims as a "5- to 7- membered ring having 1 to 6 carbon ring atoms, with the remaining ring atoms selected from oxygen and nitrogen". The group has a binding ring nitrogen, and is "linked to said group X at a ring carbon adjacent to said ring nitrogen atom", as illustrated in the specification at, for example, Fig. 3. The claim also recites possible substituents and that the ring may be fused to another ring. Examples of the latter case given in the specification include benzoxazole, benzimidazole, indole, quinoline and isoquinoline (page 9, line 28; page 15, line 18). It would be very clear to one skilled in the art whether a particular heterocyclic binding group, linked to a oxygen or nitrogen atom (group X) of the chiral component as recited, fell within the bounds of the claims.

The recitation of a "leaving group", also objected to, simply pertains to the necessary structure of a substrate on which an allylic alkylation would be performed, using the catalyst of the invention—such an alkylation involves the displacement of a leaving group. See, for example, the specification at page 12, lines 7-8 and 21. It is not necessary to specify the leaving group to define the structure of the catalyst.

In view of the foregoing, the applicants submit that the claims and specification, as amended, comply with the requirements of 35 U.S.C. §112, second paragraph.

IV. Rejections under 35 U.S.C. §103

Claims 17-23 and 53-56 were rejected under 35 U.S.C. §103 as being unpatentable over

(1) Trost and Merlic, *JACS* **112**:9590 (1990)

(2) Trost and Lautens, *Tetrahedron* **43**(21):4817 (1987)

(3) Trost and Lautens, *JACS* **109**:1469 (1987) and

(4) Trost and Murphy, *Organometallics* 4(6):1143 (1985).

The rejections are respectfully traversed in light of the following remarks.

A. The Invention

The applicants' invention, as embodied in claim 17, is directed to a catalytic composition which is useful in catalyzing enantioselective allylic alkylations. The composition is formed by contacting, in a nonprotic solvent, a chiral ligand with a hexacoordinate complex of a metal selected from tungsten(0),

disclosure of any chiral ligands.

(4) Trost and Murphy, *Organometallics* 4(6):1143 (1985)

This reference describes enantioselective allylic alkylations using a palladium complex having various chiral ligands, including binaphthyl phosphine- (6) and binaphthyl phosphinate-based ligands (7 and 11). The maximum e.e. reported with these ligands was 69%. In none of these ligands is the chiral component (the binaphthol moiety) linked to a heterocyclic binding group having a binding ring nitrogen atom, as presently claimed. Nor does the reference describe molybdenum, tungsten or chromium complexes.

C. Analysis

Of the four references cited, three of them disclose no chiral ligands whatsoever and are not directed to the goal of asymmetric synthesis; that is, producing a product having a high enantiomeric excess (e.e.). The reference that does employ chiral ligands (reference (4)) employs a palladium complex having chiral ligands in which the binding moiety is a phosphorus atom, as noted above. Therefore, even if one were to employ these ligands with a metal selected from Mo, W, or Cr, this would not produce the present invention, in which the binding groups of the chiral ligands are nitrogen heterocycles.

As stated in *In re Jones*, CAFC 1992, 958 F2d 347, 21 USPQ2d 1941, the prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound. There is no motivation in the prior art to prepare complexes of the chiral ligands recited in the claims with any metal for use in catalysis. Nor would one have predicted that the claimed compositions, if they were prepared, would produce very high e.e.'s in alkylation of a variety of substrates, as shown by the applicants.

V. Conclusion

In view of the foregoing, the applicants submit that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 324-0880.

No fees are believed due with this communication. However, the Commissioner is hereby authorized and requested to charge any deficiency in fees herein to Deposit Account No. 04-0531.

Respectfully submitted,

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Date: 10-16-2000

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